Methylphenidate for cancer related fatigue (CRF) in palliative cancer patients. Who and how for benefit ? A literature review

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Background and introduction

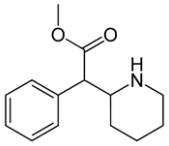
«Why does my body feel so washed out all the time»?

«I am exhausted for no reason at all»

« I wake up just as tired as when I went to sleep»

« I feel that I am losing myself»

Methylphenidate (Mph)

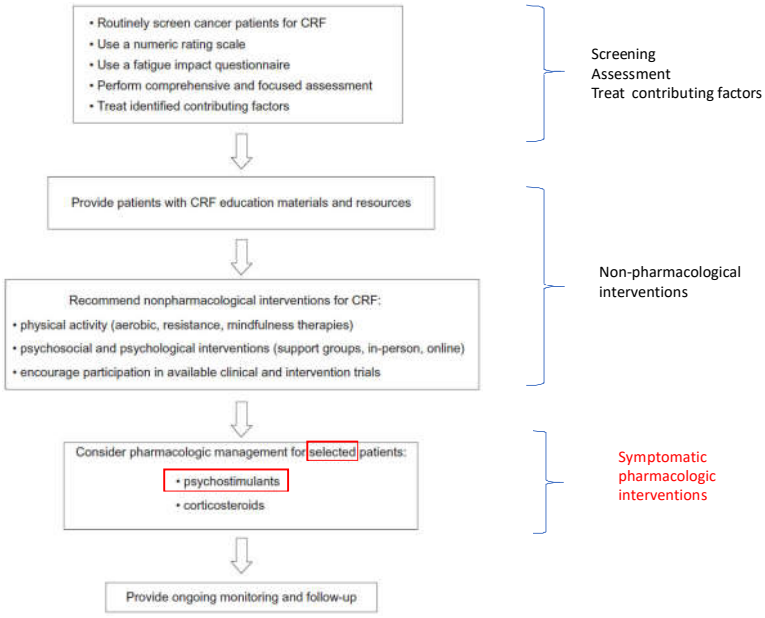


- The most studied psychostimulant agent for CRF
- Ritalin
- Dopamine-and norepinephrine reuptake inhibitor → neurotransmission ↑
- Used off-label for CRF in USA / Europe /some Scandinavian centres

- Methylphenidate in Norway:
- Approved for ADHD and narcolepsy
- Not adressed in national palliative cancer care guideline
- Not off-label CRF-tradition

CRF management

NCCN Clinical Practice Guideline



Adapted from NCCN Clinical Practice Guidelines. *Cancer-Related Fatigue*. Version 2.2018. Available from: http://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf.

Aims and objectives

Review of the literature for evidence of patient characteristics and other factors associated with benefit from Methylphenidate for fatigue symptoms in palliative cancer population ;

«Who and how for benefit ?»

Method and material

Inclusion criteria

P : Cancer patients, palliative , no treatment restrictions
I : Methylphenidate treatment
C : Placebo control
O : Fatigue as primary outcome, PROM .

Literature search

Jan. 2007 - Nov. 2017
Electronic database search (Embase, PubMed, Psych Info)
Handsearch (Ref.lists, textbooks, UpToDate-sections)
No "Grey literature" or protocol search , no author contact

Selection, extraction , quality assessment

Selection : RCTs. Prisma flowchart.
Study quality : 6-domain RoB-evaluation
QoE rating : Modified GRADE-criteria

Analysis/synthesis

Qualitative approach. No statistics.

Search terms and strategy

#	Search terms	Results	Type
1	exp advanced cancer/	69042	Advanced
2	exp methylphenidate/	20049	Advanced
3	1 and 2	97	Advanced
4	exp fatigue/ or exp cancer fatigue/	190088	Advanced
5	3 and 4	58	Advanced
6	cancer*.tw.	2034309	Advanced
7	neoplasm*.tw.	156163	Advanced
8	carcinoma*.tw.	760547	Advanced
9	1 or 6 or 7 or 8	2572066	Advanced
10	Methylphenidate.tw.	8604	Advanced
11	Ritalin.tw.	3193	Advanced
12	2 or 10 or 11	20592	Advanced
13	9 and 12	624	Advanced
14	fatigue*.tw.	121374	Advanced
15	asthen*.tw.	11113	Advanced
16	4 or 14 or 15	229794	Advanced
17	13 and 16	301	Advanced
18	(palliative or advanced or terminal).tw.	976650	Advanced
19	9 and 18	283543	Advanced
20	12 and 16 and 19	109	Advanced

Results

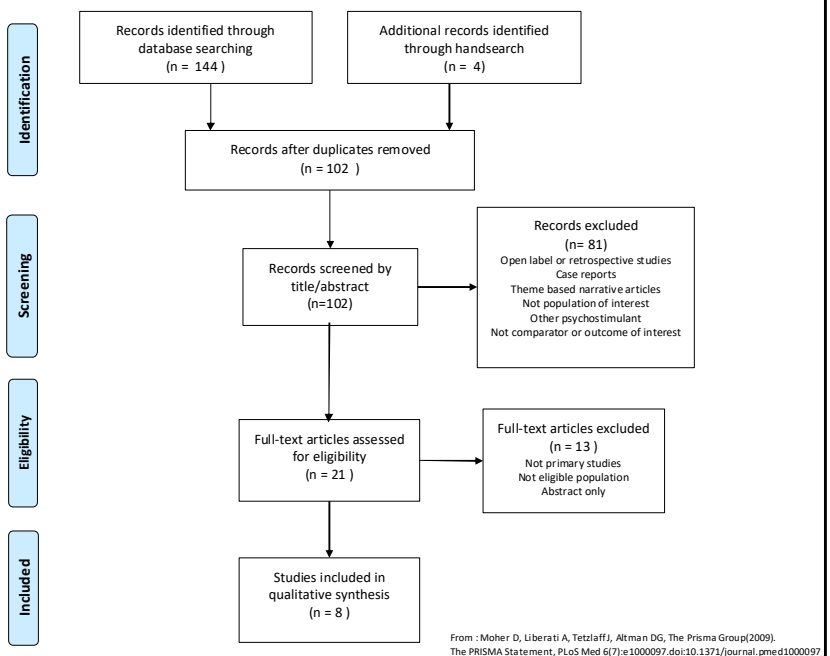


Fig 1: Identification and selection of studies

1.author, year (country)	Journal	Design	No. of subjects	Age % females	Fatigue instrument (validation instr.)	Drop- out	Result , Primary Outcome (fatigue)	Quality of study
Bruera et al, 2013 (USA)	J of Clinical Oncology	Double-blind RCT	No. 190	57,5 y (25-84) F 66%	FACIT-F subscale (ESAS-F)	25%	Significant improvement both arms No significant difference (p = 0.69)	Low
Butler et al, 2007 (USA)	Int J Radiation Oncology Biol. Phys.	Double-blind RCT	No. 68	56 y (28-83) F 45%	FACIT-F subscale	53%	No significant change any arm, no difference (p = 0,64)	Very low
Kerr et al, 2012 (USA)	J of Pain and Symptom Management	Double-blind RCT	No. 34	74 y (51-90) F 66%	Piper Fatigue Scale (ESAS-F, VAS-F)	12%	Mph significantly superior in all 3 scales (p < 0,05) No change in controls	Low
Lower et al, 2009 (USA)	J of Pain and Symptom Management	Double-blind RCT	No. 152	52,8 y (SD 9,3) F 94%	FACIT-F subscale	14%	Signifcant improvement both arms Mph significantly superior (p < 0,02)	High
Michell et al, 2015 (Australia)	J of Pain and Symptom Management	Aggreg. N-of-1 crossover 3-cycle RCT. Double-blind	No. 43 (129 cycles)	71 y (36-91) F 47%	FACIT-F subscale (Wu Cancer Fatigue Scale)	43% subjects, 33% cycles	Over-all no significant difference (p = 0,89) . 25% individual responders, Mph significantly superior	Moderate
Moraska et al, 2010 (USA)	J of Cllinical Oncology	Double-blind RCT	No. 148	60 y (SD12) F 60%	Brief Fatigue Inventory «usual fatigue» subscale	17%	Significant improvement both arms. Over-all no significant difference (p = 0,32) Mph significantly superior in strata «Most advanced cancer» and «Most severe fatigue 8-10» (p = 0,02)	Low
Richard et al, 2015 (Canada)	BJU International	Double-blind RCT	No. 24	66 y (59-75) F 0%	FACIT-F subscale (Bruera Fatigue Scale)	4%	Mph significantly superior (p = 0,02) No change in controls	Low
Roth et al, 2010 (USA)	Cancer	Double-blind RCT	No. 32	70 y (SD 9) F 0%	Brief Fatigue Inventory (Fatigue Severity Scale)	28%	Significant improvement both arms BFI total : no significant difference (p = 0,,07) BFI severity : Mph significantly superior (p = 0,03).	Low
Total 8 RCTs		**Double-blind**	**No = 691 4 x <50 p.**	**Mean age 60 y. F 62 %**	**8 diff. instruments . 5 x FACIT-F subscale 2 x Brief Fatigue Inv**	**4 trials > 20% drop-out**	**Placebo effect in 4 trials. Significant over-all difference in 3 trials. Sub-set difference in 3 trials**	**Low (separate table)**

Table 2: Quality assessment of individual studies

	Risk of bias- domains							Other quality domains				Quality rating of study
Study	Random sequence generation	Alloc. conceal-ment	Blinding participants/ personel	Blinding outcome assessment	Incomplete outcome data	Study size	Selective reporting	Eligibility criteria specified	Balance arms at baseline	Adequate statistics present.	Tools valid/ reliable	
Bruera 2013	Low	Low	Unclear	Unclear	High	Unclear	_	Yes	Yes	Yes	Yes	**Low**
Butler 2007	Unclear	Unclear	Low	Unclear	High	High	_	Yes	Yes	Yes	Yes	**Very low**
Kerr 2012	Unclear	Unclear	Low	Unclear	Low	High	_	Yes	Yes	Yes	Yes	**Low**
Lower 2009	Low	Low	Low	Low	Low	Unclear	_	Yes	Yes	Yes	Yes	**High**
Michell 2015	Low	Low	Low	Low	Unclear	Unclear	_	Yes	Yes	Yes	Yes	**Moderate**
Moraska 2010	Low	Low	Unclear	Unclear	Unclear	Unclear	_	Yes	Yes	Yes	Yes	**Low**
Richard 2015	Low	Unclear	Unclear	Low	Low	High	_	Yes	Yes	Yes	Unclear	**Low**
Roth 2010	Low	Unclear	Low	Low	Unclear	High	_	Yes	Yes	Yes	Yes	**Low**

Adapted from Cochrane Risk of Bias tool, Higgins and Altman, 2008

Total evidence quality

Rated by simplified GRADE criteria : LOW QUALITY

Reasons to downgrade:

Validity threats

Imprecision

* Publication bias not assessed

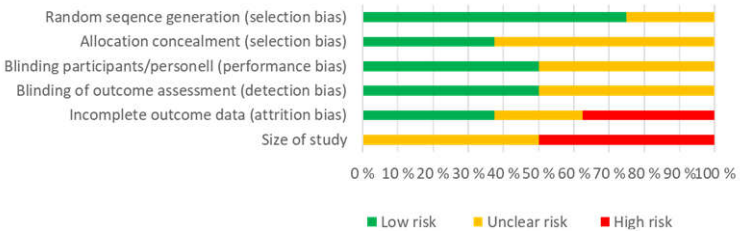


Figure 2
Distribution of risk of bias across domains

Patient exclusion criteria

Fig 3: Spectrum of exclusion criteria , % of total sample

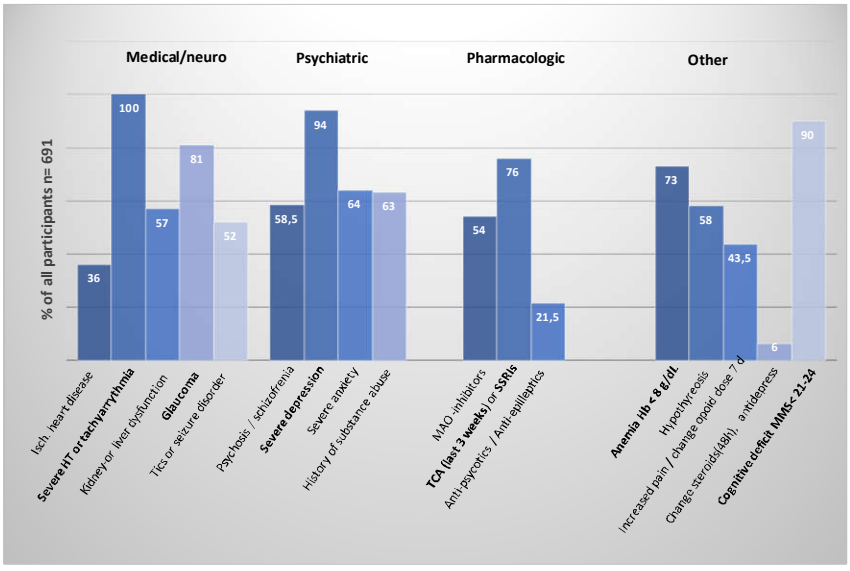


Table 3. Clinical characteristics and intervention details

Clinical characteristics | Intervention details

Study (No)	Types of cancer	Clinical setting	Baseline fatigue	Performance status	Drug, regime	Dose	Mean adm. Dose	Duration
Bruera et al, 2013 (190)	Mixed tumor (GI + lung)	PC+ onc. dep, Outpatient Onc treatment unclear	Moderate	ECOG/KPS unclear	Mph IR as needed	5mg ev 2h, max 20mg/d	6mg (4-11,8)	2 weeks
Butler et al, 2007 (68)	Brain tumor (primary, metastatic)	Brain radiation therapy (pBRT/WBRT)	Mild	ECOG 0-1 KPS >70	d-Mph , titration Profylactic	5mgx2 incr to 15mgx2 (= d-l –Mph 10mgx2 → 30mg x2)	Unknown	8 weeks post-RT
Kerr et al, 2012 (34)	Mixed tumor	Hospice, In-and outpatient Onc treatment unclear	Moderate + severe	Mean KPS 57	Mph IR, titration	5mgx2 incr by 10mg ev 3d, max 40mg/d	20mg by day 14	2 weeks
Lower et al, 2009 (152)	Mixed tumor (breast + ovarie)	Cytotoxic chemo Life exp> 6mnts	Moderate	ECOG 0-1(2)	d-Mph , titration	5mgx2 incr by 10mg ev 7d, max 50mg/d	25 mg (= d-l-Mph 50mg)	8 weeks
Michell et al, 2015 (43)	Mixed tumor	PC. dep. End-stage cancer No onc treament	Severe	KPS 60 (40-90)	Mph IR, fixed dose	5mgx2	5mgx2	3 cycles of 2x3 days
Moraska et al, 2010 (148)	Mixed tumor	Mixed pall. stage 94% onc. treatment	Moderate + severe	ECOG/KPS unclear	Mph SR, titration	18mgx1, incr by 18mg ev 7d, max 54mg/d	Unknown	4 weeks
Richard et al, 2015 (24)	Prostate cancer	LHRH-agonist Mixed pall. stage Outpatient	Moderate	ECOG/KPS unclear	Mph IR, fixed dose	5mgx1 first 2w, then 5mgx2	5mgx2	10 weeks
Roth et al, 2010 (32)	Prostate cancer	ADT +/- chemo Onc. outpatient	Moderate + severe	ECOG/KPS unclear	Mph IR, titration	5mgx1, incr by 5mg ev 3d , max 30mg/d	Unknown	6 weeks
Summary 8 trials (N = 691)	**2 x Ca.prostata 1 x Brain tumor 5 x Mixed**	**Diverse. 60 % oncol. treatment**	**Moderate and severe**	**4 x unclear 4 x ECOG 0-2**	**5 x Mph IR 1 x Mph SR 2 x d-Mph**	**8 different regimes 5x titration, 2x Fixed, 1x as need.**	**Range 6 to 50 mg daily (d-l Mph)**	**2 – 10 weeks**

Benefit associated characteristics

- Far advanced disease
- Severe baseline fatigue (FACIT-F subscale, BFI, Piper FS)

- Ongoing/recent palliative chemotherapy
- Androgen deprivation therapy (ADT) for prostate cancer

- Mph dose above 5mg x 2 (minimum) , dose titration
- Treatment duration at least 3-4 weeks (time to sep from placebo effect)

- No association to age or gender.
- No systematic association between required dose and other factors

Adverse events – dose dependant

Dose d-l Mph	AE	Mph vs placebo	Drop out due to AE
Low dose (10mg) + **Medium dose** (up to 30mg)	**Insomnia** **Nausea** Mood swings Various pain	No difference in AE rate or severity	Minimal No difference between arms
High dose (> 30mg)	**Anorexia** **Nervousness/ agitation** Dry mouth Diarrea Abd.pain Dizzieness Headache Hypertension Takycardia	Higher AE rate and intensity in Mph-arms No serious AE	Higher drop out rate in Mph-arm

Table 4: Relationship of adverse events to Mph-dose

Discussion

Insufficient / lacking data in material

- Uniform cancer groups
- Key clinical factors
  - Perf. status, nutritional status, CRF-associated symptoms, medication.

Variability in patient exclusion criteria

- Sample not a clearly defined group - heterogeneity in population.

Measurement and multi-dimensionality

- Instruments sensitive to multi-dimentional spectrum of CRF ?

Safety / AE - Mph appear well tolerated

- Supported by retrospective safety reviews
  - Hardy SE, 2009 : *Well tolerated among medically ill older adults (age 65-90)*
  - Lasheen W. et al, 2010 : *Very low risk severe AE.*
  - Andrew BN et al, 2017 : *Tolerance developement for certain AE (agitation, anorexia , dizzieness)*

Review limitations

- One person for study selection, data extraction and quality assessement
- Literature search not exhaustive
- Reporting bias and publication bias not assessed
- Secondary outcomes not analyzed
- No statistical analysis

Conclusion

Limited evidence, low quality

WHO ?
Suggest Mph for CRF be reserved to
* the most severely fatigued
* advanced cancer stage
* patients receiving palliative chemo
* patients receiving ADT for prostate cancer

Life expectancy at least 3-4 weeks

HOW ?
Dose : 10 – 30mg daily, split morning and noon.

Duration : No studies performed to support use beyond 10 weeks.

SAFETY.
Mph seem well tolerated within dose range. No serious adverse events

Trial of Mph seem as a safe option when failure of other interventions.

Acknowledgements

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Last but not least : My family !

Need for further research

- High quality RCTs on CRF in separate cancer types
- Duration beyond "placebo phase"
- Studies designed and powered to determine pre-specified predictors for fatigue improvement to Mph
- Might add value to apply multi-dimensional fatigue instruments

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Ongoing/protocolled trials :

* Metastatic melanoma , anti PD1 imm.therapy (MDACC , Houston, Texas)
* Prostate cancer (MDACC, Houston , Texas)
* Haematological cancer (Odense University Hospital, Denmark)

Attachments

Cancer-related fatigue (CRF)

«Cancer-related fatigue is a distressing, persistent subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment, that is not proportional to recent activity and interfere with usual functioning»

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines. *Cancer-Related Fatigue*. Version 2.2018

ICD-10 Criteria for Cancer-Related Fatigue

The following symptoms have been present every day or nearly every day during the same two-week period in the past month:

A. Significant fatigue, diminished energy or increased need to rest, disproportionate to any recent change in activity level; plus five or more of the following:

1. Complaints of generalized weakness, limb heaviness.
2. Diminished concentration or attention.
3. Decreased motivation or interest to engage in usual activities.
4. Insomnia or hypersomnia.
5. Experience of sleep as unrefreshing or nonrestorative.
6. Perceived need to struggle to overcome inactivity.
7. Marked emotional reactivity (e.g., sadness, frustration, irritability) to feeling fatigued.
8. Difficulty completing daily tasks attributed to feeling fatigued.
9. Perceived problems with short-term memory.
10. Postexertional fatigue lasting several hours.

B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.

C. There is evidence from the history, physical examination or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.

D. The symptoms are not primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder or delirium.

Adapted from: National Cancer Institute Web site. Fatigue (PDQ). Available at: http://www.cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional/page4. Accessed February 7, 2005.

Fatigue instruments

Table 5. Fatigue measurement instruments in selected studies

Instrument	Scale profile /scoring	Time span	Scale properties
FACIT-F subscale (1)	**13-item subscale of FACIT-F** , score 0-4. Total range 0- 52 points (higher score, less fatigue). **Diagnostic cut-off 34 p**. MID 4 points. Developed for cancer patients.	Past 7 d	Uni-dimentional Fatigue severity and interference.
Brief fatigue Inventory (BFI)	Screening + 9 items. Fatigue past week Y/N. 3q severity (now/usual/worst). 6q interference (activity, mood, relations). NRS 0-10. Code : 1-3 Mild, 4-6 Moderate, 7-10 Severe	Now/ last 24h	Uni-dimentional. Screening. Fatigue severity and interference.
ESAS-F	Fatigue NRS 0-10	Now	Uni-dimensional. Fatigue severity.
Piper Fatigue scale (PFS)	22 items, NRS 0-10. 4 subscales; Behavioral, affective, sensory, cognitive/mood. Code : 1-3 Mild, 4-6 Moderate, 7-10 Severe	Now	Multi-dimentional
VAS-F (Lee fatigue scale)	18 items, 0-100 mm. Fatigue measured as average of 13 item subscale. Validated for adults 18-55 y.	Now	Fatigue severity
Fatigue severity scale (FSS)	9 items, score 1-7 (7 worst). Focus on inteference with physical function, work, family, social life. Validated for cancer	Past 7 d	Interference and impact
Bruera Global Fatigue scale (BFS)	10 point scale. Items ?	?	?
Wu Cancer fatigue scale (WuCFS)	9 items , scale 0-5 points	Yesterday	Uni-dimentional

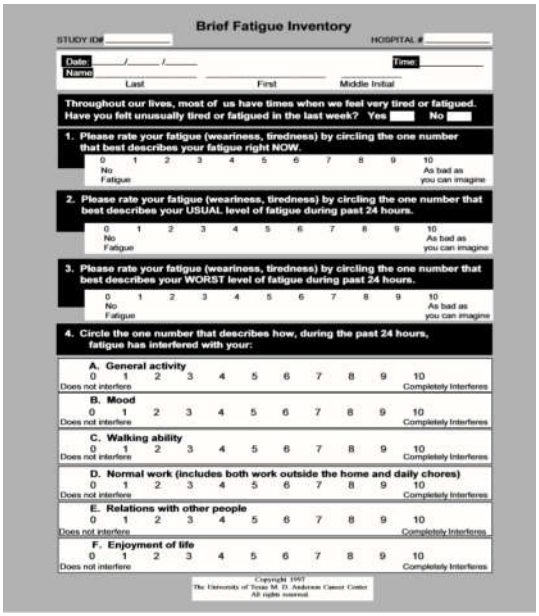
(1) Functional Assessment of Chronic Illness Therapy – Fatigue subscale (former FACT-F subscale)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
H7	I feel fatigued	0	1	2	3	4
H12	I feel weak all over	0	1	2	3	4
As1	I feel listless ("washed out")	0	1	2	3	4
As2	I feel tired	0	1	2	3	4
As3	I have trouble starting things because I am tired	0	1	2	3	4
As4	I have trouble finishing things because I am tired	0	1	2	3	4
As5	I have energy	0	1	2	3	4
As7	I am able to do my usual activities	0	1	2	3	4
As8	I need to sleep during the day	0	1	2	3	4
As12	I am too tired to eat	0	1	2	3	4
As14	I need help doing my usual activities	0	1	2	3	4
As15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
As16	I have to limit my social activity because I am tired	0	1	2	3	4

Ref: The FACIT Administration. Facit.org/Questionnaires



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ___/___/___ Time: _____

Name: _____ Last _____ First _____ Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

Quality assessment method

Quality of individual studies :

6 domain Risk of bias –evaluation ; high/low/unclear RoB
4 additional quality domains

eligibility criteria, baseline balance, tools, statistics

Aggregated ratings → global quality rating of study

Quality scale	Criteria
High quality	No high risk , 1 unclear risk
Moderate quality	No high risk, 2 unclear risk
Low quality	1 high risk or No high risk, 3 unclear risk
Very low quality	2 or more high risk